deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D-38124, Braunschweig, Germany under Accession No. DSM ACC2388 on February 16, 1999.

Please replace the paragraph at page 18, lines 26 through 30 with the following paragraph:

As can be ascertained in the Figure, it turned out that the polyclonal anti-Mcm3 rabbit antibody revealed, besides the expected prominent main protein band with an apparent molecular weight of 105 kDa, further proteins in the molecular weight range between 50 kDa and 90 kDa.

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i - iii).

In the Claims

Please cancel Claims 44 and 45 without prejudice to their prosecution in a continuation or divisional application.

## REMARKS

Paragraph 2: Restriction Requirement

Applicants acknowledge that the Examiner has maintained the restriction requirement.

Paragraph 5: Abstract of the Disclosure

As required by 37 C.F.R. § 1.72(b), an abstract of the disclosure has been added. Support for the abstract is found throughout the specification, for example, at page 2, line 18 to page 3, line 23; and page 4, line 3 to page 15, line 7.

Paragraph 6: Information Disclosure Statement

Applicants' Information Disclosure Statements (IDSs), filed February 22, 2002, February 25, 2002 and May 3, 2002 (Papers Nos. 6, 7 and 8, respectively), are acknowledged at page 3 of the Office Action. However, only initialed copies of the PTO-1449 filed February 25, 2002 (1 sheet) and the PTO-1449 filed May 3, 2002 (1 sheet) were attached to the Office Action. As such, it appears that only Paper Nos. 7 and 8 were entered and considered. Entry and consideration Paper No. 6 (IDS, Form PTO-1449 (5 sheets)) are respectfully requested. For convenience, copies of Paper No. 6 and the postcard receipt indicating receipt of this document by the Patent Office are attached hereto as Exhibit 1.

In addition, although the Examiner indicates that "the references cited in the Search Report of PCT/US00/02910 have been considered, but will not be listed on any patent resulting from the subject application because they were not provided on a separate list in compliance with 37 C.F.R. 1.98(a)(1)", it is assumed that the Examiner has, in fact, considered the references cited in the Search Report of PCT/EP00/02910.

It is noted that the references cited in the Search Report of PCT/EP00/02910 correspond to references AU, AV and AW5 cited in the IDS filed on February 22, 2002 (Paper No. 6). As such, the references cited in the Search Report of PCT/EP00/02910 were provided on a separate list in compliance with 37 C.F.R. § 1.98(a)(1).

Paragraph 7: Trademarks

The Examiner notes the use of the trademark SurfZAP® at page 7, line 35 and the trademark CELLocate® at page 20, line 1 and indicates that these marks should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology.

It is noted that the trademarks SurfZAP® and CELLocate® are already accompanied by the ® symbol and by the generic terminology wherever it appears in the application.

Paragraph 8: Objection to Disclosure

The disclosure has been objected to because the terms "Mcm3", "MCm3", McM3" and "MCM3" are used interchangeably.

As requested by the Examiner, to provide consistency, the specification has been amended to use the term "Mcm3".

Paragraph 10: Rejection of Claim 26 Under 35 U.S.C. § 112, Second Paragraph

Claim 26 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically, the Examiner alleges that recitation of the phrase "same properties" in Claim 26 renders the claim indefinite because "[i]t is unclear what properties are contemplated."

Claim 26 has been amended to recite "same binding properties", thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

Paragraph 12: Rejection of Claims 25-29, 31, 39 and 43-47 Under 35 U.S.C. § 112, First Paragraph

Claims 25-29, 31, 39 and 43-47 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner states that the hybridoma DSM ACC2388 is required to practice the invention, and, as such, it must be known and readily available to the public, obtainable or available by a repeatable method set forth in the specification or deposited in accordance with 37 C.F.R. §§ 1.801-1.809. The Examiner indicates that a Statement under 37 C.F.R. §§ 1.806 and 1.808 is required if a deposit has been made under the terms of the Budapest Treaty.

It is noted that Claims 25, 28, 39 and 43-47 do not recite the hybridoma cell line DSM ACC2388. Rather, Claims 25, 28, 39 and 43-47 recite a monoclonal antibody specific for human Mcm3.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented

in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The specification provides methods for producing monoclonal antibodies specific for human Mcm3 and evidence that monoclonal antibodies specific for human Mcm3 are produced using the described methods (see, e.g., page 5, line 20 to page 9, line 15; and page 15, line 16 to page 17, line 33). For example, the specification discloses that monoclonal anti-Mcm3 antibodies can be produced by immunizing an animal with human Mcm3, fusing the spleen cells of the immunized animals with myeloma cells and screening the resulting hybridomas for production of a monoclonal antibody specific for human Mcm3. The specification also discloses that monoclonal anti-Mcm3 antibodies can be identified and isolated by screening a recombinant combinatorial immunoglobulin library with human Mcm3 (page 7, lines 27-31).

In Examples 1 and 2, Applicants provide evidence that monoclonal antibodies specific for human Mcm3 are identified using the methods described in the specification. Applicants have thus demonstrated that monoclonal antibodies specific for human Mcm3 are produced when following the written disclosure.

Thus, armed with the teachings in the specification, it would have been a routine matter for one skilled in the art to produce monoclonal antibodies specific for human Mcm3. Accordingly, Applicants submit that the guidance provided in the specification is sufficient to enable the skilled artisan to make and use the full scope of the monoclonal anti-Mcm3 antibodies encompassed by Claims 25, 28, 39 and 43-47.

Regarding Claims 26, 27, 29 and 31, it is noted that these claims recite the hybridoma cell line DSM ACC2388. The specification discloses that the hybridoma cell line DSM ACC2388 was deposited on February 16, 1999 at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Braunschweig, Germany under Accession No. DSM ACC2388 (see page 4, lines 22-27; and page 17, lines 29-33). In accordance with 37 C.F.R. § 1.809, the specification has been amended at page 4 and page 17 to recite the address of the DSMZ.

The DSMZ is a recognized International Depositary Authority under the Budapest Treaty. The biological deposit of hybridoma cell line DSM ACC2388 (also referred to as Mcm3 (clone 101)) at the DSMZ was made under the provisions of the Budapest Treaty, and a copy of the DSMZ Budapest Treaty Deposit Receipt and Viability Statement is attached hereto (Exhibit 2). Further, a Statement Under 37 C.F.R. § 1.806 and § 1.808 is being filed concurrently, completing the formalities for deposit.

Accordingly, reconsideration and withdrawal of this aspect of the rejection of Claims 25-29, 31, 39 and 43-47 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Claims 44 and 45 have also been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, "the specification does not reasonably provide enablement for a method for the production of a preparation for the therapy of tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reactions of transplantations" using a monoclonal antibody specific for human Mcm3 or for "any pharmaceutical composition comprising any monoclonal antibody specific for human Mcm3 together with a pharmaceutical acceptable adjuvant". Paper No. 11, at page 4, lines 25-30.

In an effort to advance prosecution in the subject application, and without acquiescing to the Examiner's rejection or waiving the right to prosecute Claims 44 and 45 in the future, Claims 44 and 45 have been canceled, thereby obviating this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

Paragraph 12: Rejection of Claims 25, 26, 28, 30, 39 and 43-45 Under 35 U.S.C. § 103(a)

Claims 25, 26, 28, 30, 39 and 43-45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsuruga *et al.* (*Biochem. Biophys. Research Comm.*, 236:118-125 (1997)) in view of Harlow *et al.* (*Antibodies: A Laboratory Manual* (1998)) and U.S. Patent No. 5,876,438.

*Teachings of the Cited References*

Tsuruga *et al.*

Tsuruga *et al.* is cited by the Examiner as teaching "polyclonal antibodies (MBL) to synthesized peptides (EEEKSQEDQEQKRKRRRKTRQPDAK) corresponding to residues No. 677-700 of human Mcm3 (HsMcm3)". Paper No. 11, at page 6, lines 16-18. Although Tsuruga *et al.* report that their antibodies against HsMcm3 were "monospecific, recognizing only a single band at the expected size on SDS-PAGE gels" (see, e.g., page 119, column 2, second full paragraph), the results in Figures 1A and 1B actually reveal that their antibodies against HsMcm3 recognize two protein bands, a protein band of about 105 kDa and a protein band between 50-90 kDa. Importantly, Tsuruga *et al.* considered their antibodies "to be of sufficient quality for Western blot analyses" (see, e.g., page 119, column 2, second full paragraph) and "useful for immunoprecipitation" (see, e.g., page 119, column 2, third full paragraph). Accordingly, Tsuruga *et al.* teach away from producing monoclonal antibodies specific for human Mcm3.

Moreover, polyclonal antibodies are structurally and functionally different from the monoclonal antibodies. In particular, polyclonal antibodies do not possess the structural and functional specificity of monoclonal antibodies. A polyclonal antibody can bind a multiplicity of different epitopes on the immunizing antigen, while monoclonal antibodies bind to a specific epitope. Accordingly, the monoclonal antibodies of the present invention are structurally and functionally different from the polyclonal antibody against HsMcm3 taught by Tsuruga *et al.*

Harlow *et al.*

The Harlow *et al.* reference is a laboratory manual that provides general methods for producing monoclonal antibodies. Harlow *et al.* do not teach or suggest producing a monoclonal antibody specific for human Mcm3.

U.S. Patent No. 5,876,438 ('438)

The '438 patent does not cure the deficiencies of the Tsuruga *et al.* and the Harlow *et al.* references. The '438 patent relates to intraocular devices for treatment and/or prevention of secondary cataracts and methods for their production and use. The intraocular devices are said to comprise at least one cytotoxic agent capable of binding specifically to lens epithelial cells (see, e.g., column 2, lines 30-31). The cytotoxic agent is said to be typically a conjugate of a protein macromolecule capable of binding to lens epithelial cells, particularly a conjugate of a monoclonal antibody capable of binding lens epithelial cells (see, e.g., column 6, lines 17-24). Methods for producing monoclonal antibodies capable of binding lens epithelial cells are provided (see, e.g., columns 6-8). No where is it taught in the '438 patent that monoclonal antibodies specific for human Mcm3 can be used in the intraocular devices.

Importantly, the '438 patent does not teach or suggest producing a monoclonal antibody specific for human Mcm3. The '438 patent does not even mention human Mcm3.

*The Combination of References*

In support of the rejection, the Examiner alleges that it would have been prima facie obvious to one of ordinary skill in the art "to produce monoclonal antibody using the method taught by Harlow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and screen the resultant hybridoma cells by radioimmunoassay and immunohistochemical staining as taught by the '438 patent". Paper No. 11, at page 7, lines 15-19. The Examiner alleges that one of ordinary skill "would have been motivated to do so because the monoclonal antibodies produced exhibit a high degree of specificity, homogeneity and ability to be produced in unlimited quantities as taught by Harlow *et al.* and the screening methods will allow the identification of the hybridoma of interest with the desired specificity as taught by '438 patent." Paper No. 11, at page 7, lines 20-24.

Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital

Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Notwithstanding the above, a *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

If a compound is claimed, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. In re Deuel, 34 U.S.P.Q.2d 1210, 1214 (Fed. Cir. 1995). Thus, a key issue is whether the teachings of the cited art had established, to a reasonable degree of certainty, the claimed compounds (monoclonal antibody specific for human Mcm3, hybridoma cell line expressing a monoclonal antibody specific for human Mcm3, diagnostic or pharmaceutical composition comprising a monoclonal antibody specific for human Mcm3).

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S.P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

None of the cited references (Tsuruga *et al.*, Harlow *et al.*, '438 patent), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, would have suggested a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. None of the cited references, alone or in combination,

would have suggested a hybridoma cell line expressing a monoclonal antibody specific for human Mcm3 or a process for producing a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. None of the cited references, alone or in combination, would have suggested a diagnostic or pharmaceutical composition comprising a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Tsuruga *et al.* teach polyclonal antibodies specific for HsMcm3 that were considered to be of sufficient quality for Western blot analyses and useful for immunoprecipitation. As such, Tsuruga *et al.* teach away from producing monoclonal antibodies specific for human Mcm3. Harlow *et al.* teach general methods for producing monoclonal antibodies, but do not teach or suggest producing monoclonal antibodies for human Msm3. The '438 patent teaches intraocular devices for treatment and/or prevention of secondary cataracts and provides methods for producing monoclonal antibodies capable of binding lens epithelial cells for use in the intraocular devices. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Further, even assuming, *arguendo*, that a *prima facie* case of obviousness exists, which it does not, the *prima facie* case of obviousness would be overcome by a showing of unexpected results. It is well settled that a patent applicant can rebut a *prima facie* case of obviousness by a showing of "unexpected results", e.g., by showing that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. See, e.g., In re Soni, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995).

As discussed above, polyclonal antibodies are structurally and functionally different from monoclonal antibodies. Polyclonal antibodies do not possess the structural and functional specificity of monoclonal antibodies. As shown in the application (Figure), a comparison of a monoclonal anti-Mcm3 antibody of the present invention and a polyclonal anti-Mcm3 antibody by Western blotting demonstrates that the monoclonal antibody recognizes only one protein band at 105 kDa, the molecular weight for Mcm3, while the polyclonal antibody recognizes both the 105 kDa protein band and additional protein bands with apparent molecular weights between 50 and 90 kDa.

Additionally, Applicants have demonstrated the unexpected results that at antibody concentrations between 0.15 to 6.0 mg/L, monoclonal anti-Mcm3 antibodies perform better than the polyclonal anti-Mcm3 antibodies in detecting the presence of Mcm3 protein both in normal tissue and tumor tissue (see Birner, P. *et al.*, *Am. J. Pathol.*, 158:1991-1996 (2001), particularly Figures 1A and 1B; attached hereto as the Exhibit 3).

Accordingly, even assuming, *arguendo*, that a *prima facie* case of obviousness exists, which it does not, it has been overcome by Applicants' unexpected results. Reconsideration and withdrawal of the rejection of Claims 25, 26, 28, 30, 39 and 43-45 under 35 U.S.C. § 103(a) are respectfully requested.

Paragraph 13: Rejection of Claim 46 Under 35 U.S.C. § 103(a)

Claim 46 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsuruga *et al.* in view of Harlow *et al.* and U.S. Patent No. 4,281,061 ('061).

*Teachings of the Cited References*

The Tsuruga *et al.* and Harlow *et al.* references are discussed above.

The '061 patent does not cure the deficiencies of the Tsuruga *et al.* Harlow *et al.* reference. The '061 patent is cited by the Examiner as teaching that "reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest". Paper No. 11, at page 8, lines 6-8. The '061 patent provides methods, compositions and kits for performing "homogeneous immunoassays". Importantly, the '061 patent does not teach or suggest a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3. The '061 patent does not even mention human Mcm3.

*Combination of References*

In support of the rejection, the Examiner alleges that it would have been prima facie obvious for one of ordinary skill in the art "to produce monoclonal antibody using the method taught by Harlow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and include the monoclonal antibody in a kit format as taught by the '061 patent." Paper No. 11, at page 8, lines 9-12. The Examiner alleges that one of ordinary skill in the art "would have been motivated to do so because such kits are provided for a matter of convenience and to optimize the sensitivity of the assay in the range of interest as taught by '061 patent." Paper No. 11, at page 8, lines 13-15. Applicants respectfully disagree that Claim 46 is obvious in view of the cited art.

The Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. As such, the rejection is improper.

Notwithstanding the above, none of the cited references (Tsuruga *et al.*, Harlow *et al.*, '061 patent), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, would have suggested a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Tsuruga *et al.* teach polyclonal antibodies specific for HsMcm3 that were considered to be of sufficient quality for Western blot analyses and useful for immunoprecipitation. As such, Tsuruga *et al.* teach away from producing monoclonal antibodies specific for human Mcm3. Harlow *et al.* teach general methods for producing monoclonal antibodies, but do not teach or suggest producing monoclonal antibodies for human Msm3. The '061 patent teaches methods, compositions and kits for performing "homogeneous immunoassays", but does not teach or suggest a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3. Accordingly, the teachings of the cited references, either alone or in combination, would not have established, to a reasonable degree of certainty, the monoclonal antibodies specific for human Mcm3 or diagnostic kits comprising a monoclonal antibody

specific for human Mcm3 of the present invention. The cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of the rejection of Claim 46 under 35 U.S.C. § 103(a) are respectfully requested.

Paragraph 14: Rejection of Claim 47 Under 35 U.S.C. § 103(a)

Claim 47 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsuruga *et al.* in view of Harlow *et al.*, U.S. Patent No. 4,281,061 ('061) and further in view of U.S. Patent No. 6,316,208 ('208).

*Teachings of the Cited References*

The Tsuruga *et al.* and Harlow *et al.* references, as well as the '061 patent, are discussed above.

The '208 patent does not cure the deficiencies of the Tsuruga *et al.* and Harlow *et al.* references and the '061 patent. The '208 patent is cited by the Examiner as teaching "antibodies p27 and Ki-67 used for immunostaining" and "for histologic grade and assays of p27, Ki-67 proliferation index in tumor cells and expression level". Paper No. 11, at page 9, lines 11-14. The '208 patent provides methods for determining the relative amount of p27 protein in a cell. Importantly, the '208 patent does not teach or suggest a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3.

*Combination of Reference*

In support of the rejection, the Examiner alleges that it would have been prima facie obvious for one of ordinary skill in the art "to produce monoclonal antibody using the method taught by Harlow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and combined the monoclonal antibody Mcm3 with antibodies Ki-67 and p27 taught by the '208 patent in a diagnostic kit as taught by the '061 patent". Paper No. 11, at

page 9, lines 15-19. The Examiner alleges that one of ordinary skill in the art "would have been motivated to do so because the combined Mcm3 antibody with the antibodies p27 and Ki-67 to characterize the proliferation of tumor cells as taught by the '208 patent and the expression nuclear localization of Mcm3 during cell cycle as taught by Tsuruga *et al.*" Paper No. 11, at page 9, lines 20-23. Applicants respectfully disagree that Claim 47 is obvious in view of the cited art.

As above, the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. As such, the rejection is improper.

Notwithstanding the above, none of the cited references (Tsuruga *et al.*, Harlow *et al.*, '061 patent, '208 patent), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, would have suggested a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Tsuruga *et al.* teach away from producing monoclonal antibodies specific for human Mcm3. Harlow *et al.* teach general methods for producing monoclonal antibodies, but do not teach or suggest producing monoclonal antibodies for human Msm3. The '061 patent teaches methods, compositions and kits for performing "homogeneous immunoassays", but does not teach or suggest a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3. The '208 patent teaches methods for determining the relative amount of p27 protein in a cell, but does not teach or suggest a monoclonal antibody specific for human Mcm3 or a diagnostic kit comprising a monoclonal antibody specific for human Mcm3. Accordingly, the teachings of the cited references, either alone or in combination, would not have established, to a reasonable degree of certainty, the monoclonal antibodies specific for human Mcm3 or diagnostic kits comprising a monoclonal antibody specific for human Mcm3 of the present invention. The cited references, either alone or in combination, would not have reasonably suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of the rejection of Claim 47 under 35 U.S.C. § 103(a) are respectfully requested.

Paragraphs 16 and 17: Drawings

A new formal Figure is being filed concurrently herewith.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____

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Concord, MA 01742-9133
Dated: April 21, 2003

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 3, lines 16 through 23 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Also, within the scope of the invention are methods for treating diseases or disorders which are associated with an aberrant [McM3] Mcm3 level or activity or which can benefit from modulation of the activity or level of [McM3] Mcm3. The methods comprise administering, e.g., either locally or systemically to a subject, a pharmaceutically effective amount of a composition comprising an [MCm3] Mcm3 antibody according to the present invention.

Replace the paragraph at page 3, lines 27 through 34 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

[Fig. 1] The Figure shows a Western Blot using a monoclonal antibody according to the present invention (right side) and a polyclonal antibody known in the art (left side). It is clearly demonstrated that the antibody according to the present invention recognises only one band while the polyclonal antibody detects further bands in the range of 90 to 50 kDa. H denotes HeLa cells and C denotes CHO cells.

Replace the paragraph at page 4, lines 22 through 27 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A hybridoma cell line producing a preferred monoclonal antibody of the present invention, namely, a monoclonal mouse antibody with said above-mentioned detection, was deposited at the Deutsche[n] Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D-38124, [in] Braunschweig, Germany under [the number] Accession No. DSM ACC2388 on February 16, 1999.

Replace the paragraph at page 5, lines 11 through 14 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A disease, a disorder or condition "associated with" or "characterized by" an aberrant [McM3] Mcm3 activity refers to a disease, disorder or condition in a subject which is caused by or contributed to by an aberrant [MCm3] Mcm3 activity.

Replace the paragraph at page 14, line 27 through page 15, line 7 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Performing combined staining of tissues detecting the three proteins simultaneously, allow a more detained assessment of cell proliferation and differentiation processes that determine individual tumor growth. [MCM3] Mcm3 protein is expressed in cells that have ceased to proliferate, but are not terminally differentiated according to the absence of p27 protein expression, whereas Ki-67 is expressed in proliferating cells only. P27 can be found in quiescent cells but not in proliferating cells. Ki-67, [MCM3] Mcm3 and p27 provide one set of parameters which define complementary biological properties that are suitable for a detailed characterization of disordered cell growth and tumorgenesis. Tumor diagnostics may also benefit from a combined assessment of these markers which may be of help to choose the most appropriate therapy concept for an individual patient.

Replace the paragraph at page 17, lines 26 through 33 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Hybridoma which were positive both in the spot-blot and in immunohistology, were cloned and recloned until they were monoclonal. Independent monoclonal antibodies were obtained. A hybridoma cell producing a monoclonal antibody according to the invention was deposited at the Deutsche[n] Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D-38124, [in] Braunschweig, Germany under [number] Accession No. DSM ACC2388 on February 16, 1999.

Replace the paragraph at page 18, lines 26 through 30 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As can be ascertained in the Figure [Fig. 1], it turned out that the polyclonal anti-Mcm3 rabbit antibody revealed, besides the expected prominent main protein band with an apparent molecular weight of 105 kDa, further proteins in the molecular weight range between 50 kDa and 90 kDa.